Pergamon

Tetrahedron Letters 40 (1999) 2071–2074

TETRAHEDRON
LETTERS

N-Methylanilines from Benzylic Azides

Francisco J. Lopez* and Dov Nitzan

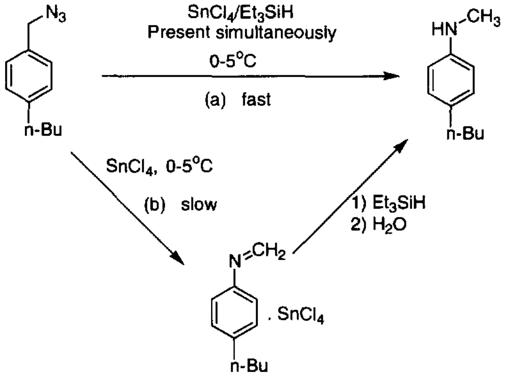
Discovery Medicinal Chemistry, Neurobiology Unit
Roche Bioscience, 3401 Hillview Ave, Palo Alto, CA, 94304 USA.

Received 30 October 1998; accepted 22 December 1998

Abstract: Benzylic azides are converted into *N*-methylanilines efficiently in the presence of a Bronsted or Lewis acid and Et_3SiH. The combination of $SnCl_4/Et_3SiH$ and 4-*n*-butylbenzyl azide appears to form an aminodiazonium trichlorostannate(II), which undergoes the rearrangement to an iminium salt that is then reduced to *N*-methyl-4-*n*-butylaniline by Et_3SiH. © 1999 Elsevier Science Ltd. All rights reserved.

The rearrangement of benzylic azides to *N*-arylimine derivatives has been known for quite some time.[1] Thus, acid catalysis,[2] thermal,[3] irradiation[4] and free radical[5] conditions have been used. Also related is the Schmidt reaction on benzylic alcohols with hydrazoic acid.[6] However, direct transformation of benzylic azides to *N*-alkylanilines would be very desirable. Toward this objective, Pearson[7] and Aubé[8] have shown very recently that benzyl azide rearranges to give tetrahydroquinolines on treatment with triflic acid and alkenes, and α-(phenylaminomethyl)ketones on treatment with triflic acid and ketones, respectively.

In this report, we would like to describe a general conversion of benzylic azides to *N*-methylanilines in the presence of a Bronsted or Lewis acid and triethylsilane. For example, treatment of 4-*n*-butylbenzyl azide with $SnCl_4$ and Et_3SiH at 0-5°C in CH_2Cl_2 gives *N*-methyl-4-*n*-butylaniline in 91% yield. It is notable that the reaction appears to be accelerated in the presence of Et_3SiH under these conditions; that is, path (a) (Scheme), in which both reagents are present simultaneously, is much faster than the stepwise path (b). In the presence of $SnCl_4$ alone, some starting azide persists even after 20 h; however, when Et_3SiH is subsequently added, the azide transformation is complete within a few minutes. In another experiment, 81% of the starting azide was recovered after being in contact with $SnCl_4$ for 3 hours; whereas the presence of Et_3SiH from the beginning resulted in consumption of the azide in less than 30 minutes.



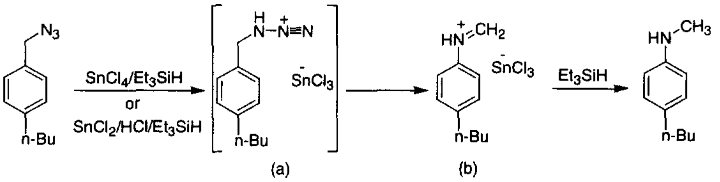
The relative amounts of Et_3SiH and $SnCl_4$ are critical to achieve complete reaction. Thus, 3-3.3 equiv of Et_3SiH and 2 equiv of $SnCl_4$ seem to be necessary for a complete conversion. Fewer equiv of Et_3SiH results in lower yield and recovery of the starting azide.

PII: S0040-4039(99)00148-3

In order to reach an understanding of the mechanism, some additional considerations were taking into account. It is known that equimolar amounts of trialkylsilanes and $SnCl_4$ form $SnCl_2$, R_3SiCl and HCl according to eq 1 (R=Et).[9] Indeed, addition of $SnCl_4$ to Et_3SiH in CH_2Cl_2 at 0-5°C forms a white suspension with evolution of HCl (g). Filtration of the white solid gives 94% of $SnCl_2$.[10] The same reaction, but in CD_2Cl_2, gives a clean formation of Et_3SiCl by ^{1}H NMR.

$$Et_3SiH + SnCl_4 \longrightarrow Et_3SiCl + SnCl_2 + HCl \qquad (1)$$

Treatment of 4-*n*-butylbenzyl azide with the products of eq 1, that is HCl (g), or $SnCl_2$, or Et_3SiCl in combination with Et_3SiH does not promote any formation of 4-*n*-butyl-*N*-methylaniline. However, the benzylic azide in the presence of both HCl (g) and $SnCl_2$, in addition to Et_3SiH, does undergo the desired conversion to 4-*n*-butyl-*N*-methylaniline.[11] It appears that the combination of HCl/$SnCl_2$ with the benzylic azide forms the reactive species aminodiazonium trichlorostannate(II) **a** (eq 2)[12] that undergoes the rearrangement to the iminium salt **b**, which is then reduced to the *N*-methylaniline by Et_3SiH.[13] Therefore, the transformation of the benzylic azide in the presence of $SnCl_4$ and Et_3SiH appears to follow the mechanism shown below.



(2)

Table 1 shows the results of the conversion of 4-*n*-butylbenzyl azide to *N*-methyl-4-*n*-butylaniline with different Lewis acids. $SnCl_4$ and triflic acid give the best results (entries 1-2). As expected, from the work of Pearson[7] and Aubé[8], triflic acid alone is capable of inducing the rearrangement to the iminium intermediate (**b**, eq 2, $^-$OTf instead of $^-SnCl_3$) which is then reduced to the *N*-methylaniline by Et_3SiH. $TiCl_4$ and BF_3 give lower yields (entries 3 and 5), mainly because of side reactions in the former case,[14] and a greatly reduced reaction rate in the latter instance.

Table 1. Rearrangement of 4-*n*-butylbenzyl azide to *N*-methyl-4-*n*-butylaniline[a]

Entry	Lewis Acid	Temperature °C	Time h	Yield %
1	$SnCl_4$	0-5	0.5	91
2	CF_3SO_3H	0-5	0.5	85
3	$TiCl_4$	0-5	1	28
4	$EtAlCl_2$	0-5	16	49
5	$BF_3.OEt_2$	20-25	16	27
6	CH_3SO_3H	reflux	16	42
7	Et_2AlCl	reflux	16	No reaction

(a) 2.1 equiv Lewis acid, 3.3 equiv of triethylsilane in dichloromethane.

Table 2 shows the scope of the transformation with different groups on the aromatic ring.[15] Functional groups, such as alkyl, halogen, ester, aryl, or methoxyl at position 3 give good results. The benzyl azide with a ketone carbonyl group at position 4 undergoes the transformation to the *N*-methylaniline along with reduction of the carbonyl group (entry 9). The trifluoromethyl group at position 4 results in lower conversion, with 47% recovery of starting azide (entry 5). Presence of the strong electron-donating methoxyl group at position 4 results in a mixture (entry 6),[16] and presence of the strong electron-withdrawing nitro group at position 3 or 4 prevents the reaction (entries 8 and 14).

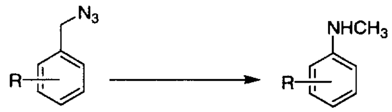
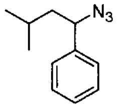


Table 2. Transformation of benzylic azides to *N*-methylanilines[a]

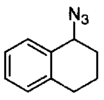
Entry	R	Yield[b] %
1	4-*n*-Bu	91
2	4-Br	63
3	4-Cl	72
4	4-Ph	83[c]
5	4-CF_3	23[d]
6	4-OMe	-[e]
7	4-CO_2Me	40[c]
8	4-NO_2	-[f]
9	4-CO(4-$NO_2C_6H_4$)	49[g]
10	3-Br	60
11	3-Cl	55
12	3-OMe	80
13	3-CO_2Me	62
14	3-NO_2	-[f]
15	3,5-DiMe	87
16	2-Me	91
17	2-Br	40

(a) 2.1 Equiv tin tetrachloride, 3.3 equiv triethylsilane in dichloromethane at 0-5°C for 0.5-3 h, unless otherwise noted. (b) Yields are based on isolated, pure compounds. All new compounds exhibited satisfactory analytical data. (c) 3.0 Equiv tin tetrachloride at 20-25°C. (d) 47% Recovered starting azide. (e) Mixture of at least 4 products, one of them the desired one (ca. 8%).[16] (f) No reaction or slow decomposition after reflux for 24 h. (g) 4.0 Equiv triflic acid, 3.0 equiv triethylsilane at 20-25°C; product is *N*-methyl-4-(4-nitrophenyl)methylaniline.

Branching at the α-position at the benzylic site (*e.g.*, **c** or **d**) gives complex mixtures under the standard conditions.

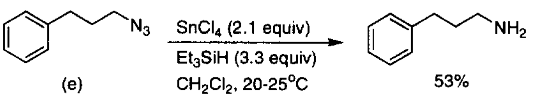


(c)



(d)

Aliphatic azides (*e.g.*, **e**) principally undergo reduction to the primary amine. This is the first report to describe this reduction under Lewis acid/triethylsilane conditions.[17]

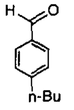


(e) 53% (3)

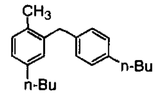
In conclusion, benzylic azides containing a range of different substituents at different positions on the aromatic ring undergo a facile conversion into *N*-methylanilines in the presence of Et_3SiH and either $SnCl_4$ or triflic acid. An aminodiazonium trichlorostannate(II) species is proposed to account for the fast rearrangement of benzylic azides in the presence of both Et_3SiH and $SnCl_4$.

References and Notes

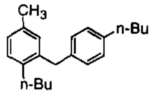
1. a) Scriven, E. F.; Turnbull, K. *Chem. Reviews* **1988**, *88*, 297. b) Abramovitch, R. A.; Kyba, E. P. In *The Chemistry of the Azido Group*, Patai, S. Ed.; Wiley: New York, 1971; Chapter 5. c) Banthorpe, D. V. In *The Chemistry of the Azido Group*, Patai, S. Ed.; Wiley: New York, 1971; Chapter 7.
2. a) Adam, G.; Andrieux, J.; Plat, M. *Tetrahedron* **1985**, *41*, 399. b) Adam, G.; Andrieux, J.; Plat, M. *Tetrahedron Lett.* **1981**, *22*, 3181. c) Arcus C. L.; Marks, R. E.; Coombs, M. M. *J. Chem Soc.* **1957**, 4064. d) Bhatt, M. V. *Chem. Ind.* **1956**, 1390.
3. a) Leeson, P. D.; Carling, R. W.; James, K.; Baker, R. *J. Org. Chem.* **1990**, *55*, 2103. b) Takeuchi H.; Eguchi, S. *J. Chem. Soc. Perkin Trans. I* **1988**, 2149. c) Radinov, R.; Haimova, M.; Simova, S.; Simova, E. *Liebigs Ann. Chem.* **1988**, 231. d) Ohkata, K.; Mase, M.; Akiba, K. *J. Chem. Soc. Chem. Commun.* **1987**, 1727. e) Desbene, P-L.; Jehanno, N. *J. Heterocycl. Chem* **1984**, *21*, 1313, 1321. f) Le Roux, J-P.; Desbene, P-L.; Cherton, *J. Hetrocycl. Chem.* **1981**, *18*, 847.
4. a) Mascal, M.; Wood, I. G.; Begley, M. J.; Batsanov, A. S.; Walsgrove, T.; Slawin, A. M. Z.; Williams, D. J.; Drake, A. F.; Siligardi, G. *J. Chem. Soc. Perkin Trans. I* **1996**, *20*, 2427. b) Mascal, M.; Moody, C. J.; Morrell, A. I.; Slawin, A. M. Z.; Williams, D. J. *J. Amer. Chem. Soc.* **1993**, *115*, 813. c) Wayne, G. S.; Snyder, G. J.; Rogers, D. W. *J. Amer. Chem. Soc.* **1993**, *115*, 9860. d) Mascal, M.; Moody, C. J.; Slawin, A. M. Z.; Williams, D. J. *J. Chem. Soc. Perkin Trans. I* **1992**, *7*, 823.
5. Kim, S.; Do, J. Y. *J. Chem. Soc. Chem. Commun.* **1995**, 1607.
6. a) Pearson, W. H.; Gallagher, B. M. *Tetrahedron* **1996**, *52*, 12039. b) Pearson, W.H.; Fang, W. *J. Org. Chem.* **1995**, *60*, 4960. c) Alberici, G. F.; Andrieux, J.; Adam, G.; Plat, M. M. *Tetrahedron Lett.* **1983**, *24*, 1937. d) Adam, G.; Andrieux, J.; Plat, M. *Tetrahedron Lett.* **1983**, *24*, 3609. e) Adam, G.; Andrieux, J.; Plat, M. *Tetrahedron* **1982**, *38*, 2403. f) Duong, T.; Prager, R, H.; Were, S. T. *Aust. J. Chem.* **1983**, *36*, 1431.
7. Pearson, W. H.; Fang, W. *Isr. J. Chem.* **1997**, *37*, 39.
8. Schildknegt, K.; Agrios, K. A.; Aubé, J. *Tetrahedron Lett.* **1998**, *39*, 1998.
9. Voronkov, M. G.; Skorik, Y. I. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1964**, 1215.
10. Melting point (248°C) and Raman spectrum were identical to a sample from a commercial source (Aldrich Chemical Co).
11. At slower rate than that using the original conditions ($SnCl_4$/Et_3SiH), though. This might be attributable to the more diluted conditions used with HCl/$SnCl_4$/Et_3SiH (0.04 M in CH_2Cl_2 vs 0.16 M used with $SnCl_4$/Et_3SiH) and/or the quality of $SnCl_2$.
12. For examples of formation of the trichlorostannate(II) ion from $SnCl_2$/HCl see: a) Bulten, E. J.; Van den Hurk, J. W. G. *J. Organomet. Chem.* **1978**, *162*, 161. b) Parshall, G. W. *Inorg. Synth.* **1974**, *15*, 222. Investigation on the formation of the trichlorostannate(II) ion from Et_3SiH/$SnCl_4$ is underway.
13. Triethylsilane/trifluoroacetic acid has been utilized to reduce *N*-arylimines: a) Masaru, T.; Asawa, Y.; Igarashi, M. *J. Heterocycl. Chem.* **1997**, *34*, 973. b) Kursanov, D. N.; Parnes, Z. N.; Loim, N. M. *Synthesis* **1974**, 633.
14. By-products such as i, ii and iii were detected.



i

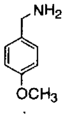


ii

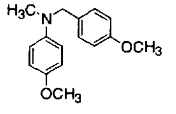


iii

15. Representative description: To a solution of 4-*n*-butylbenzyl azide (108 mg, 0.57 mmol) in CH_2Cl_2 (2.4 mL) was added tin tetrachloride (1.2 mL of 1M solution in CH_2Cl_2) at 0-5°C under argon. After 5-10 minutes, triethylsilane (0.3 mL, 1.88 mmol) was added. The resulting white suspension was stirred at 0-5°C for 30 minutes. 10% sodium hydroxide was added at 0-5°C. Mixture was allowed to reach 20-25°C, stirred 10 minutes and extracted with CH_2Cl_2 (3 x 5-10 mL). Extract was washed with water, dried (Na_2SO_4) and concentrated to dryness. Purification by preparative TLC (92:8 hexane/ethyl acetate) gave a colorless oil (85 mg, 91% yield). ^1H NMR (200 MHz, $CDCl_3$) δ 0.91 (t, 3H, *J*=7.3 Hz), 1.33 (m, 2H), 1.55 (m, 2H), 2.50 (t, 2H, *J*=7.6 Hz), 2.82 (s, 3H), 3.4-3.6 (br, 1H), 6.56 (m, 2H), 7.01 (m, 2H); EIMS *m/z* 163 (24, M^+), 120 (100).
16. Other products such as iv (13%) and v (34%) were isolated.



iv



v

17. For reviews of other methods see: a) Gilchrist, T. L. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I. Eds.; Pergamon Press: Oxford, UK, 1991; Vol. 8, pp. 381-402. b) Ref. 1a. c) Sheradsky, T. In *The Chemistry of the Azido Group*, Patai, S. Ed.; Wiley: New York, 1971; Chapter 6.